Hypoproteinemia and Cystic Fibrosis

D. W. NEBERT, M.S., M.D., AND
D. D. CURTIS, M.D., *Los Angeles*

INADEQUATE INTAKE of protein or renal disease account for the majority of instances of hypoproteinemia and edema in infancy.[1] Edema as a result of hypoproteinemia is a rare occurrence in patients with cystic fibrosis of the pancreas.

Fleisher and coworkers reported four cases and reviewed 22 additional instances of hypoproteinemia and edema in children who had cystic fibrosis of the pancreas; they implicated human milk or soybean milk feedings as factors responsible for hypoproteinemia in infants with cystic fibrosis.[2] In the majority of reported cases, pulmonary infections and anemia developed and the patients died between eight and 16 weeks of age.

In the present case, the patient had hypoproteinemic edema at seven and a half months of age and there were other atypical features of cystic fibrosis.

Report of a Case

A 33-week-old Caucasian girl was admitted to UCLA Hospital on 3 December 1964, because of swelling of the face for one week and swelling of the legs for two days. Her health had been deteriorating since an episode of moniliasis one month before admission, which had been successfully treated.

The patient weighed 5 pounds 13 ounces at birth after an uneventful 37-week gestation and 18 hours of labor. Vertex delivery was difficult and the baby did not cry spontaneously at birth. She was in an isolette for three days with "respiratory problems," but results of roentgen and blood studies were not abnormal.

After one month on breast milk alone, the baby weighed only 5 pounds 14 ounces. When changed to cow's milk formula, the infant had considerable spitting up, wheezing, gagging and frequent loose stools. Her diet was changed to soybean-base formula at four months of age.

The patient had become increasingly irritable and anorexic after the bout of thrush at 29 weeks of age. There was colicky pain associated with passage of one large bulky stool daily. When questioned, the mother stated the stools were usually foul-smelling and sometimes floated on water. A week before the baby was admitted to hospital the mother noted puffiness of the eyelids and cheeks. When the extremities became edematous and the parents noticed the baby was urinating less frequently, her physician recommended that she be put in hospital immediately.

Many paternal relatives had asthma and "respiratory" problems. The only sibling, a 2½-year-old brother, had had two bouts of pneumonia (at seven months and 24 months of age), plus severe diarrhea and wheezing at age nine months. Although results of three sweat tests during his stays in hospital were equivocal, his present health was excellent.

The patient had puffy cheeks and pitting edema

Department of Pediatrics, School of Medicine, University of California, Los Angeles.
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of all extremities. The skin was pale. The pulse rate was 160. She could not sit unaided and was so irritable that she preferred to lie undisturbed on her back.

Results of blood cell count and urinalysis were within normal limits. Hemoglobin was 13.2 gm per 100 ml. Roentgenograms ruled out infantile cortical hyperostosis. Serum protein was diminished; the albumin:globulin ratio was 1.9:1.4 gm per 100 ml. The electrophoretic pattern was normal. Serum glucose, alkaline phosphatase, electrolytes, calcium, phosphorus and creatinine were within normal limits. Serum copper was borderline low. The glucose tolerance curve was normal. Three stools had greatly increased fat and starch content, were negative trypsin activity and had a pH of 6.5. A stool was negative for enteropathogens. Sweat chlorides were 116 and 142 mEq per liter by the body-bagging technique.[8] Repeat value by the iontophoresis method[4] was 111 mEq per liter.

A regimen of Viokase® with each feeding and a high protein diet with skim milk and multivitamins was begun. The edema subjectively improved, appetite increased and the child became much less irritable after five days of treatment.

One week after she was discharged from the hospital, pneumonitis developed. Throat culture showed a predominance of *Neisseria* and *Staphylococcus aureus;* chlortetracycline therapy (30 mg per kilogram of body weight per day, with good response. At 10 months of age the child was eating well and had no edema. She was continued on a high-protein, high-calorie diet, multivitamins, Viokase® and chlortetracycline.

Discussion

This patient is unusual in that she presented with edema at seven months of age. In only three of the 26 reported cases[2] did the onset of edema occur later than six months. In contrast to our patient, the majority of these infants were also anemic when the diagnosis was established.

While the pathogenesis of anemia is unknown in cases of hypoproteinemic edema, intracellular copper and protein are important to the bone marrow in erythropoiesis: copper as a metal in enzyme and cytochrome structure, protein for new cell synthesis. Serum copper can be low in cases of severe edema, but this does not reflect the total body content of copper and cannot be directly related to anemia.

The diagnosis of cystic fibrosis was made in this patient at the time of severe edema and low serum protein. It has been reported that two infants with cystic fibrosis of the pancreas had normal sweat chlorides while they were edematous and hypoproteinemic.[5] The explanation of this phenomenon is unknown but must be related to the basic problem of hypoproteinemic edema. Edema is usually produced by a relative reduction in the osmotic pressure of plasma proteins in relation to the hydrostatic pressure in the capillaries. It is said that edema appears when the serum albumin concentration falls below 2.5 gm per 100 ml.[6]

Hypoalbuminemia in children with mucoviscidosis may be the result of an increased plasma volume linked to congestive heart failure.[7] Pittman and coworkers studied only three children, however, and they tried to correlate *in vivo* findings of increased plasma volume with rather tenuous postmortem changes suggestive of heart failure. Except for edema, there was no evidence of heart failure in the present case.

At 33 weeks of age this patient's gammaglobulin concentration was 170 mg per 100 ml; the accepted physiologic, low-normal gammaglobulin levels of infancy are 200 to 400 mg per ml. In the defense mechanisms to fight infection, the relative production and destruction of serum gammaglobulins and the types (γ^A, γ^G or γ^M) of globulins are more important factors than absolute serum gammaglobulin measurements.[9] Thus, we cannot say hypogammaglobulinemia or hypoproteinemic edema of cystic fibrosis specifically lowers one's defenses against infections.

The patient in the present case had difficulty in her first month of life on breast milk, as well as the serious edema while on soybean-base formula. Nitrogen balance studies have shown that soybean-base formula and breast milk are poor sources of protein for an infant with cystic fibrosis of the pancreas.[3] The pathogenesis of hypoproteinemia in this patient is most likely related to failure to absorb significant nitrogen from soybean milk or breast milk. Decided reduction of edema followed the institution of a high-protein diet, skim milk and oral pancreatic enzymes.

Hypoproteinemic edema and cystic fibrosis are likely to become an increasingly common iatrogenic entity. The physician dealing with feeding difficulties of infancy should not substitute soybean-base formula or continue breast milk feeding without realizing that the infant with cystic

fibrosis will develop life-threatening hypoproteinemic edema.

Summary

A diagnosis of cystic fibrosis of the pancreas was made in a 33-week-old infant who presented with hypoproteinemic edema. The pathogenesis and complications of hypoproteinemia were discussed.

Department of Pediatrics, U.C.L.A. School of Medicine, Los Angeles, California 90024 (Nebert).

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